EXHIBIT I

Impurities found in certain angiotensin II receptor blocker (ARB) products, also known as sartans

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Overview

In the summer of 2018, several valsartan products were recalled in Canada and worldwide because of the impurity, N-nitrosodimethylamine (NDMA), found in the active ingredient manufactured by Zhejiang Huahai Pharmaceuticals in China.

Since that time, NDMA and other similar impurities, N-nitrosodiethylamine (NDEA), N-Nitrosodiisopropylamine (NDIPA) and N-Nitrosomethyl-n-butylamine (NMBA), have been found in valsartan or other drugs in the same class as valsartan (referred to as angiotensin II receptor blockers or ARBs) made by several different manufacturers in different countries and has prompted additional recalls in Canada and worldwide.

ARBs are used to treat patients with high blood pressure to help prevent heart attacks and stroke. NDEA, NDMA, NDIPA and NMBA are nitrosamines that are classified as probable or potential human carcinogens, which means that long-term exposure could increase the risk of cancer. Since the risk of cancer is with long-term exposure, there is no immediate health risk associated with the use of ARBs containing these impurities.

Health Canada recognizes the stress caused by this issue to Canadians who rely on these important medications. The Department has been working with companies and international regulatory partners to determine the root cause of the issue and to verify that appropriate actions are taken to prevent it from happening again.

Health Canada continues to hold manufacturers responsible for the safety and effectiveness of drugs sold on the Canadian market and has taken several actions to mitigate the risk to Canadians, including:

- Requested, confirmed and monitored the effectiveness of recalls due to this issue. A list of recalled products is provided below and will be updated as needed.
- Communicated the recalls, NDMA risk estimates, and Health Canada actions to Canadians on several occasions.
- Contacted all market authorization holders of all ARBs of concern in Canada and assessed the manufacturing processes they use to make products sold in Canada.
- Determined that the Chuannan site of Zhejiang Huahai Pharmaceuticals and Hetero Laboratories Limited, Unit 1 are Non-Compliant with Good Manufacturing Practices requirements. This means that no products can be imported from those sites, unless they are considered medically necessary.
- Tested samples of ARBs on the Canadian market. Test results are provided below and will be updated as additional test results become available.
- Requested market authorization holders of ARBs of concern test all products currently on the market and any new products not yet released for NDEA and NDMA. Companies were also requested to consider using manufacturing practices that avoid the generation and presence of all nitrosamine impurities. This added safeguard will provide greater assurance of the safety of ARBs in Canada.

Health Canada continues to work closely with international regulatory partners, including the US Food and Drug Administration and the European Medicines Agency, to share information and coordinate efforts on inspections, risk assessments and public communications. We will continue to take action and update Canadians should any new risks be identified for products on the Canadian market.

Recalls

Health Canada is publishing a complete list of angiotensin II receptor blocker (ARB) products recalled in Canada due to the presence of or the potential for nitrosamine impurities. This list will be updated if new products are recalled. Products not on this list have **not** been recalled in Canada due to this issue. It should be noted that recalls taking place in other countries may not impact Canadian products.

Patients taking recalled medications should:

- Continue taking your medication **unless** you have been advised to stop by your health care provider.
- Contact your health care provider to discuss treatment options if you have been using an affected product.
- Ask your pharmacist if you are unsure whether you are taking a recalled product.
- Contact your health care provider if you have taken a recalled product and you have concerns about your health.

List of recalled products:

Product name/Active Pharmaceutical Ingredient	DIN	Strength	Lot #	Date Recalled	API Manufacturer
AURO-IRBESARTAN/HCT	02447878	150/12.5 mg	IN1518001-A	April 17, 2019	Aurobindo Pharma Limited, Unit-I
PRO DOC LIMITEE - IRBESARTAN	02365200	150 mg	604292	March 11, 2019	TEVA API India Ltd.
PRO DOC LIMITEE - IRBESARTAN	02365219	300 mg	601795	March 11, 2019	TEVA API India Ltd.
APO-LOSARTAN	02379058	25 mg	NL1453	March 8, 2019	Hereto Laboratories Limited Unit 1
APO LO ARTAN	02379058	25 mg	NL1452	March 8 2019	Hereto Laboratorie Limited Unit 1
APO-LOSARTAN	02353504	50 mg	NK1254	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353504	50 mg	NK1253	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353512	100 mg	NL1461	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353512	100 mg	NG2092	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353512	100 mg	NH5932	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353512	100 mg	NH5933	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN	02353512	100 mg	NL1460	March 8, 2019	Hereto Laboratories Limited Unit 1
APO LO ARTAN	02353512	100 mg	NH5934	March 8 2019	Hereto Laboratorie Limited Unit 1
APO-LOSARTAN/HCTZ	02371235	50/12.5 mg	NL1441	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371235	50/12.5 mg	NZ8848	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371235	50/12.5 mg	NL1445	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371235	50/12.5 mg	NZ8849	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371235	50/12.5 mg	NZ8860	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371243	100/12.5 mg	NG2087	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371243	100/12.5 mg	NL1421	March 8, 2019	Hereto Laboratories Limited Unit 1
APO LO ARTAN/HCTZ	02371243	100/12 5 mg	NG2086	March 8 2019	Hereto Laboratorie Limited Unit 1
APO-LOSARTAN/HCTZ	02371243	100/12.5 mg	NL1422	March 8, 2019	Hereto Laboratories Limited Unit 1

Product name/Active Pharmaceutical Ingredient	DIN	Strength	Lot #	Date Recalled	API Manufacturer
APO-LOSARTAN/HCTZ	02371251	100/25 mg	NL1429	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371251	100/25 mg	NZ8846	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371251	100/25 mg	NZ8847	March 8, 2019	Hereto Laboratories Limited Unit 1
APO-LOSARTAN/HCTZ	02371251	100/25 mg	NZ8845	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309750	25 mg	498294	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309750	25 mg	605342	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309750	25 mg	611944	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	498285	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	600047	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	600091	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	603894	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	612025	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	612031	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	612679	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309769	50 mg	616743	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	498864	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	602668	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	603816	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	605298	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	605300	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	613935	March 8, 2019	Hereto Laboratories Limited Unit 1
PMS-LOSARTAN	02309777	100 mg	613936	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394367	25 mg	498292	March 8, 2019	Hereto Laboratories Limited Unit 1

Product name/Active Pharmaceutical Ingredient	DIN	Strength	Lot #	Date Recalled	API Manufacturer
LOSARTAN (PRO DOC LIMITEE)	02394367	25 mg	605344	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394375	50 mg	498779	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394375	50 mg	600046	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394375	50 mg	603903	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394375	50 mg	498284	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394375	50 mg	603895	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394383	100 mg	499008	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394383	100 mg	605299	March 8, 2019	Hereto Laboratories Limited Unit 1
LOSARTAN (PRO DOC LIMITEE)	02394383	100 mg	605297	March 8, 2019	Hereto Laboratories Limited Unit 1
TEVA-LOSARTAN/HCTZ	02358263	50/12.5 mg	35344801A	March 6, 2019	Hereto Laboratories Limited Unit 1
TEVA-LOSARTAN/HCTZ	02358263	50/12.5mg	35349397A	March 6, 2019	Hereto Laboratories Limited Unit 1
MYLAN-VALSARTAN	02383527	40 mg	All lots	November 28, 2018	Mylan Laboratories Limited
MYLAN-VALSARTAN	02383535	80 mg	All lots	November 28, 2018	Mylan Laboratories Limited
MYLAN-VALSARTAN	02383543	160 mg	All lots	November 28, 2018	Mylan Laboratories Limited
MYLAN-VALSARTAN	02383551	320 mg	All lots	November 28, 2018	Mylan Laboratories Limited
TEVA-VALSARTAN/HCTZ TABLETS	02356996	80/12.5 mg	35211136A	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357003	160/12.5 mg	35211335A	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357003	160/12.5 mg	35211844R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357011	160/25 mg	35210937R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357011	160/25 mg	35210938R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357011	160/25 mg	35210939R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357011	160/25 mg	35210940R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS	02357038	320/12.5 mg	35211546R	August 17, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 40MG FC TABLETS	02337487	40 mg	K47338	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 80MG FC TABLETS	02337495	80 mg	K45370	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 80MG FC TABLETS	02337495	80 mg	K47652	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 80MG FC TABLETS	02337495	80 mg	K47653	July 9, 2018	Zhejiang Huahai Pharmaceuticals

Product name/Active Pharmaceutical Ingredient	DIN	Strength	Lot #	Date Recalled	API Manufacturer
ACT-VALSARTAN 80MG FC TABLETS	02337495	80mg	K47654	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 160MG FC TABLETS	02337509	160 mg	K39691	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 160MG FC TABLETS	02337509	160 mg	K44167	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 160MG FC TABLETS	02337509	160 mg	K47657	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 160MG FC TABLETS	02337509	160 mg	K47658	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 320MG FC TABLETS	02337517	320 mg	K44166	July 9, 2018	Zhejiang Huahai Pharmaceuticals
ACT-VALSARTAN 320MG FC TABLETS	02337517	320 mg	K45371	July 9, 2018	Zhejiang Huahai Pharmaceuticals
PRO DOC LIMITEE VALSARTAN 40 MG	02367726	40 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
PRO DOC LIMITEE VALSARTAN 80 MG	02367734	80 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
PRO DOC LIMITEE VALSARTAN 160 MG	02367742	160 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
PRO DOC LIMITEE VALSARTAN 320 MG	02367750	320 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANDOZ VALSARTAN 40 MG	02356740	40 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANDOZ VALSARTAN 80 MG	02356759	80 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANDOZ VALSARTAN 160 MG	02356767	160 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANDOZ VALSARTAN 320 MG	02356775	320 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANIS VALSARTAN 40 MG	02366940	40 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANIS VALSARTAN 80 MG	02366959	80 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANIS VALSARTAN 160 MG	02366967	160 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SANIS VALSARTAN 320 MG	02366975	320 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SIVEM PHARMACEUTICAL ULC VALSARTAN 40 MG	02384523	40 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SIVEM PHARMACEUTICAL ULC VALSARTAN 80 MG	02384531	80 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SIVEM PHARMACEUTICAL ULC VALSARTAN 160 MG	02384558	160 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
SIVEM PHARMACEUTICAL ULC VALSARTAN 320 MG	02384566	320 mg	All lots	July 9, 2018	Zhejiang Huahai Pharmaceuticals
TEVA-VALSARTAN/HCTZ TABLETS PP 30s	02357046	320/25 mg	35212731R	July 9, 2018	Zhejiang Huahai Pharmaceuticals

Test Results

Health Canada has tested samples of ARBs on the Canadian market for NDMA and NDEA and the results are posted below. Health Canada will continue to assess new developments to determine whether additional testing is necessary.

The results indicate the NDMA or NDEA levels detected, whether they exceed acceptable limits, based on a lifetime exposure, and whether the product was recalled.

Health Canada's testing results:

Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad

Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
Accel Pharma Inc.	ACCEL-CANDESARTAN	02463784	32	1805003937	Alembic Pharmaceuticals Limited (API Division - II)	2020-02-29	Not Detected	Not Detected	No	No	No
Actavis Pharma Company	ACT VALSARTAN	02337517	320	K44166	Zhejiang Huahai Pharmaceutical Co., Ltd.	2018-07-31	**15242.72**	**12.78**	**Yes**	No	**Yes**
	ACT VALSARTAN	02337517	320	K45371	Zhejiang Huahai Pharmaceutical Co., Ltd.	2018-10-31	**10770.86**	**186.67**	**Yes**	**Yes**	**Yes**
	ACT- OLMESARTAN	02442205	40	F83746	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-03-31	Not Detected	Not Detected	No	No	No
Angita Pharma Inc.	AG-IRBESARTAN	02474417	300	IE317017AR	Jubilant Generics Limited	2019-10-31	Not Detected	Not Detected	No	No	No
Apotex Inc.	APO-OLMESARTAN/HCTZ	02453614	40/12.5	NF7704	Apotex Pharmachem India Pvt. Ltd.	2019-02-28	Not Detected	Not Detected	No	No	No
	APO-OLMESARTAN/HCTZ	02453614	40/12.5	NN7635	Signa S.A. de C.V.	2019-12-31	Not Detected	Not Detected	No	No	No
	APO-LOSARTAN/HCTZ	02371235	50/12.5	NL1445	Hetero Labs Limited	2019-08-31	Not Detected	Not Detected	No	No	No
	APO-LOSARTAN	02353512	100	NL1461	Hetero Labs Limited	2019-08-31	Not Detected	Not Detected	No	No	No
AstraZeneca Inc.	ATACAND - CANDESARTAN	02311658	32	KL0275	Takeda Pharmaceutical Company Limited	2021-04-30	Not Detected	Not Detected	No	No	No
Auro Pharma Inc.	AURO-CANDESARTAN HCT	02421046	32/12.5	WKSA18004-A	Aurobindo Pharma Limited & Chromo Laboratories Limited	2020-07-29	Not Detected	Not Detected	No	No	No
	AURO-IRBESARTAN	02406098	75	IA7517001-A	Aurobindo Pharma Limited- Unit 1	2020-06-30	Not Detected	4.7	No	No	No
	AURO-IRBESARTAN	02406098	75	IA7517002-A	Aurobindo Pharma Limited- Unit 1	2020-11-05	Not Detected	4.44	No	No	No
	AURO-IRBESARTAN	02406098	75	IA7517003-A	Aurobindo Pharma Limited- Unit 1	2020-11-05	Not Detected	4.61	No	No	No

* These values are based on a drug's maximum daily dose as reflected in the drug label

* The levels of nitrosamine impurities detected in this lot were very close to the acceptable limit. Health Canada determined that products from t represent a risk to the Canadian public and are considered to be safe for use.

Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
	AURO-IRBESARTAN	02406101	150	IA1517002-A	Aurobindo Pharma Limited- Unit 1	2020-10-31	Not Detected	9.77	No	No	No
	AURO-IRBESARTAN	02406101	150	IA1517001-A	Aurobindo Pharma Limited- Unit 1	2020-06-30	Not Detected	**13.63**	No	**Yes** [2]	**No** [2]
	AURO-IRBESARTAN	02406101	150	IA1517003-A	Aurobindo Pharma Limited- Unit 1	2020-10-31	Not Detected	8.97	No	No	No
	AURO-IRBESARTAN	02406128	300	IA3017001-A	Aurobindo Pharma Limited- Unit 1	2020-06-30	Not Detected	**27.81**	No	**Yes** [2]	**No** [2]
	AURO-IRBESARTAN	02406128	300	IA3017003-A	Aurobindo Pharma Limited- Unit 1	2020-10-31	Not Detected	17.47	No	No	No
	AURO-IRBESARTAN	02406128	300	IA3017002-A	Aurobindo Pharma Limited- Unit 1	2020-10-31	Not Detected	19.6	No	No	No
	AURO-IRBESARTAN HCT	02447894	300/25	IN3018001-A	Aurobindo Pharma Limited- Unit 1	2020-04-06	Not Detected	**26.78**	No	**Yes** [2]	**No** [2]
	AURO-IRBESARTAN HCT	02447886	300/12.5	IR3018001-A	Aurobindo Pharma Limited- Unit 1	2020-04-06	Not Detected	**30.29**	No	No	**This lo was n distril**
	AURO-IRBESARTAN HCT	02447878	150/12.5	IN1518001-A	Aurobindo Pharma Limited- Unit 1	2020-04-06	Not Detected	**15.82**	No	**Yes**	**Yes**
	AURO-OLMESARTAN	02443872	40	WOSB18004-A	Aurobindo Pharma Unit-I	2020-01-12	Not Detected	Not Detected	No	No	No
	AURO-LOSARTAN	02403358	100	WB1018003-A	Aurobindo Pharma Unit-I	2021-03-15	Not Detected	Not Detected	No	No	No
	AURO-VALSARTAN	02414201	40	VWSA17003-A	Aurobindo Pharma Limited, Unit-XI	2019-10-31	Not Detected	1.41	No	No	No
	AURO-VALSARTAN	02414201	40	VWSA18007-A	Aurobindo Pharma Limited, Unit-XI	2020-08-24	Not Detected	1.07	No	No	No
	AURO-VALSARTAN	02414201	40	VWSA18003-A	Aurobindo Pharma Limited, Unit-XI	2020-08-23	Not Detected	1.04	No	No	No
	AURO-VALSARTAN	02414228	80	VWSB17010-A	Aurobindo Pharma Limited, Unit-XI	2019-07-31	Not Detected	Not Detected	No	No	No

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Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
	AURO-VALSARTAN	02414228	80	VWSB17011-A	Aurobindo Pharma Limited, Unit-XI	2019-07-31	Not Detected	Not Detected	No	No	No
	AURO-VALSARTAN	02414236	160	VWSC17001-A	Aurobindo Pharma Limited, Unit-XI	2018-12-31	Not Detected	< 3.20	No	No	No
	AURO-VALSARTAN	02414236	160	VWSC17005-A	Aurobindo Pharma Limited, Unit-XI	2019-05-31	Not Detected	< 3.20	No	No	No
	AURO-VALSARTAN	02414236	160	VWSC18002-A	Aurobindo Pharma Limited, Unit-XI	2020-01-19	Not Detected	4.58	No	No	No
	AURO-VALSARTAN	02414236	160	VWSC18001-A	Aurobindo Pharma Limited, Unit-XI	2020-01-19	< 6.40	4.39	No	No	No
	AURO-VALSARTAN	02414236	160	VWSC18016-A	Aurobindo Pharma Limited, Unit-XI	2020-08-24	Not Detected	4.7	No	No	No
	AURO-VALSARTAN	02414244	320	VWSD17001-B	Aurobindo Pharma Limited, Unit-XI	2019-05-31	Not Detected	Not Detected	No	No	No
	AURO-VALSARTAN	02414244	320	VWSD18005-A	Aurobindo Pharma Limited, Unit-XI	2020-08-25	Not Detected	12.14	No	No	No
	AURO-VALSARTAN	02414244	320	VWSD18001-A	Aurobindo Pharma Limited, Unit-XI	2020-04-15	Not Detected	8.56	No	No	No
	AURO-VALSARTAN	02414244	320	VWSD18001-A	Aurobindo Pharma Limited	2020-04-15	Not Detected	8.61	No	No	No
	AURO-VALSARTAN HCT	02408112	80/12.5	HHSA18001-A	Aurobindo Pharma Limited, Unit-XI	2021-08-02	Not Detected	1.88	No	No	No
Jamp Pharma Corp	JAMP-OLMESARTAN	02461668	40	MC218002A	Glenmark Pharmaceuticals Limited	2020-04-30	Not Detected	Not Detected	No	No	No
	JAMP-LOSARTAN-HCTZ	02408252	100/25	LY218001A	Jubilant Generics Limited	2019-06-30	Not Detected	Not Detected	No	No	No
	JAMP-IRBESARTAN	02418215	300	IE318005A	Jubilant Generics Limited	2020-03-31	Not Detected	Not Detected	No	No	No

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Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
Merck Canada Inc.	OLMETEC - OLMESARTAN	02318679	40	N021852	Daiichi Sankyo Chemical Pharma Co., Ltd. Hiratsuka Plant	2020-04-30	Not Detected	Not Detected	No	No	No
Mint Pharmaceuticals Inc.	MINT-LOSARTAN/HCTZ DS	02389673	100/25	1805009844	Alembic Pharmaceuticals Limited (API Division - II)	2021-07-31	Not Detected	Not Detected	No	No	No
Mylan Pharmaceuticals ULC	MYLAN-VALSARTAN	02383527	40	3048813	Mylan Laboratories Limited, Unit 8, in Hyderabad, India	2017-11-30	< 1.60	**8.32**	No	**Yes**	**Yes**
	MYLAN-VALSARTAN	02383535	80	3056368	Mylan Laboratories Limited, Unit 8, in Hyderabad, India	2019-06-30	< 3.20	**22.43**	No	**Yes**	**Yes**
	MYLAN-VALSARTAN	02383543	160	3056371	Mylan Laboratories Limited, Unit 8, in Hyderabad, India	2019-06-30	Not Detected	**62.76**	No	**Yes**	**Yes**
	MYLAN-VALSARTAN	02383551	320	3048815	Mylan Laboratories Limited, Unit 8, in Hyderabad, India	2017-11-30	Not Detected	**132.77**	No	**Yes**	**Yes**
Novartis Pharmaceuticals Canada Inc.	DIOVAN	02289504	320	BEK32	Novartis Pharma Schweizerhalle	2021-07-31	Not Detected	Not Detected	No	No	No
Pharmascience Inc.	PMS-CANDESARTAN HCTZ	02391295	16	615170	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-04-30	Not Detected	Not Detected	No	No	No
	PMS-LOSARTAN	02309777	100	613936	Hetero Labs Limited	2021-03-31	Not Detected	10.41	No	No	No
	PMS-LOSARTAN-HCTZ	02392232	100/12.5	0803847	Dr. Reddy's Laboratories Limited	2020-06-30	Not Detected	Not Detected	No	No	No
	PMS-IRBESARTAN	02317087	300	615908	Zhejiang Tianyu Pharmaceutical Co., Ltd.	2021-03-31	Not Detected	Not Detected	No	No	No
	PMS-IRBESARTAN-HCTZ	02328526	300/12.5	606524	Zhejiang Tianyu Pharmaceutical Co., Ltd.,	2018-11-30	Not Detected	Not Detected	No	No	No

* These values are based on a drug's maximum daily dose as reflected in the drug label

* The levels of nitrosamine impurities detected in this lot were very close to the acceptable limit. Health Canada determined that products from t represent a risk to the Canadian public and are considered to be safe for use.

Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
	PMS-IRBESARTAN-HCTZ	02328526	300/12.5	611016	USV Private Limited	2019-11-30	Not Detected	Not Detected	No	No	No
Ranbaxy Pharmaceuticals Canada Inc.	RAN-VALSARTAN	02363119	160	2884804	Sun Pharmaceutical Industries Limited	2019-05-31	Not Detected	Not Detected	No	No	No
Sandoz Canada Inc.	SANDOZ CANDESARTAN	02417340	32	JC3223	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-06-30	Not Detected	Not Detected	No	No	No
	SANDOZ CANDESARTAN PLUS	02420732	32	HY8217	Zhejiang Tianyu Pharmaceutical Co., Ltd.	2020-04-30	Not Detected	Not Detected	No	No	No
	SANDOZ OLMESARTAN	02443422	40	HX2039	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-02-28	Not Detected	Not Detected	No	No	No
	SANDOZ LOSARTAN	02313359	100	JD6746	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-04-30	Not Detected	Not Detected	No	No	No
	SANDOZ VALSARTAN	02356775	320	HW4965	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-12-31	**2703.76**	Not Detected	**Yes**	No	**Yes**
	SANDOZ IRBESARTAN	02328496	300	HX4282	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-01-31	Not Detected	Not Detected	No	No	No
	SANDOZ IRBESARTAN	02328496	300	JD1818	Zhejiang Tianyu Pharmaceutical Co., Ltd.	2020-05-31	Not Detected	Not Detected	No	No	No
Sanis Health Inc.	IRBESARTAN	02372398	300	35213058A	TEVA API INDIA PVT. LTD.	2019-12-31	Not Detected	Not Detected	No	No	No
Sanofi-Aventis Canada Inc.	AVAPRO - IRBESARTAN	02237925	300	KC001	CHINOIN Pharmaceutical and Chemical Works Private Co. Ltd.	2020-01-31	Not Detected	Not Detected	No	No	No
Septa Pharmaceuticals Inc.	SEPTA-LOSARTAN	02424983	100	LR318004A	Jubilant Generics Limited	2020-03-31	Not Detected	Not Detected	No	No	No
Sivem Pharmaceuticals Inc.	LOSARTAN HCT	02388987	100/25	QX1018005-B	Zhejiang Tianyu Pharmaceutical Co., Ltd.	2021-06-08	Not Detected	Not Detected	No	No	No
	IRBESARTAN	02385309	300	HX7687	Zhejiang Huahai Pharmaceutical Co., Ltd.	2019-12-31	Not Detected	Not Detected	No	No	No

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* The levels of nitrosamine impurities detected in this lot were very close to the acceptable limit. Health Canada determined that products from t represent a risk to the Canadian public and are considered to be safe for use.

Market Authorization Holder (Company) Name	Product Name	DIN	Strength (mg)	Lot Number	API Manufacturer	Expiry Date	NDMA Result ng / tablet	NDEA Result ng / tablet	NDMA Limit (96 ng/day) Exceeded? *	NDEA Limit (26.5 ng/day) Exceeded? *	Recal Canad
	IRBESARTAN HCT	02385325	300/12.5	HY7380	Zhejiang Huahai Pharmaceutical Co., Ltd.	2020-11-30	Not Detected	Not Detected	No	No	No
Teva Canada Limited	TEVA-CANDESARTAN	02366339	32	2537058	Pliva Croatia Ltd.	2020-05-31	Not Detected	Not Detected	No	No	No
	TEVA-LOSARTAN	02357976	100	2070318	Teva API India Private Ltd	2021-03-31	Not Detected	Not Detected	No	No	No
	TEVA-LOSARTAN/HCTZ	02358263	50/12.5	35349397A	Hetero Labs Limited	2020-09-30	Not Detected	10.3	No	No	No
	TEVA-IRBESARTAN	02316412	300	35213086A	TEVA API INDIA LTD	2019-12-31	Not Detected	Not Detected	No	No	No
	TEVA-VALSARTAN	02356686	320	35211729R	Jubilant Generics Limited	2019-03-31	Not Detected	Not Detected	No	No	No
	TEVA-VALSARTAN/HCTZ	02357038	320/12.5	35212732	Zhejiang Huahai Pharmaceutical Co., Ltd.	2019-10-31	**14538.35**	Not Detected	**Yes**	No	**This lo was n distril**
	TEVA-VALSARTAN/HCTZ	02357038	320/12.5	35211546R	Zhejiang Huahai Pharmaceutical Co., Ltd.	2019-01-31	**258.19**	**1770.87**	**Yes**	**Yes**	**Yes**
	TEVA-VALSARTAN/HCTZ	02357046	320/25	35212731R	Zhejiang Huahai Pharmaceutical Co., Ltd.	2019-11-30	**13367.64**	Not Detected	**Yes**	No	**Yes**

* These values are based on a drug's maximum daily dose as reflected in the drug label

* The levels of nitrosamine impurities detected in this lot were very close to the acceptable limit. Health Canada determined that products from t represent a risk to the Canadian public and are considered to be safe for use.

Test Method

Health Canada is providing a method that has been developed to detect and quantify the nitrosamine impurities N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in angiotensin II receptor blockers (ARBs).

Determination of *N* Nitrosodimethylamine (NDMA) and *N* Nitrosodiethylamine (NDEA) by GC MS MS (Direct Injection) in Sartan Finished Products and Drug Substances

1. Principle and Scope

The present method has been developed to detect and quantify the nitrosamine impurities *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA) in Valsartan, Irbesartan and Losartan finished products. The method is performed by gas chromatography-tandem mass spectrometry (GC-MS-MS) using direct injection.

The method can also be used to detect and quantify NDMA and NDEA in candesartan and olmesartan finished products, and in sartan drug substances (e.g. valsartan, irbesartan, losartan, candesartan, and olmesartan). However, if interferences are observed, further validation may be required.

2. Safety

Laboratory safety precautions are followed to ensure a safe and healthy work environment, including the use of personal protective equipment (including but not limited to a lab coat, protective eyewear, and nitrile or butyl rubber gloves) and appropriate laboratory engineering controls (e.g. containment ventilation equipment).

The chemicals used in this method are hazardous. Analysts should carefully read the Material Safety Data Sheet (MSDS) for each chemical. Due to the toxic nature of nitrosamines, it is recommended that diluted reference standard solutions be purchased in order to reduce the extent of potential exposure.

3. Reagents and Reference Standards

- Methanol, HPLC grade (CAS #: 67-56-1)
- NDMA: *N*-Nitrosodimethylamine solution (5000 µg/mL in methanol; CAS #: 62-75-9)
- NDEA: *N*-Nitrosodiethylamine solution, (100 µg/mL in methanol; CAS #: 55-18-5)
- NDMA-d6 solution: *N*-nitrosodimethylamine-d6 (1000 µg/mL in methanol; CAS #: 17829-05-9)

4. Instrument/Equipment

- Agilent GC 7890A with MSMS 7000 with EI source or equivalent
- Agilent DB-624 25 m x 0.32 µm 1.8 µm or equivalent
- 2 mL amber screw-cap GC vials with caps (PTFE/Silicone)
- 20 x 125 mm screw cap round bottom glass tubes with caps
- Automatic pipettes, various volumes
- Top-loading balance suitable for ± 0.01 g and Analytical balance suitable for ± 0.0001 g readability
- Volumetric Flasks (class A), various volumes
- Pasteur pipettes and pipette bulbs
- Spatula
- 15 mL amber glass vials with caps
- 40 mL amber glass vials with caps
- Vortex mixer, single and multi-tube
- Vial racks and storage racks
- Kimwipes
- Mortar and pestle
- Ultrasonic water bath
- Centrifuge, Beckmann-Coulter Allegra X-15R or equivalent

5. Preparation of Solutions

Standard solutions

Reference Standard Stock solutions (as purchased)

- *NDMA standard solution* in Methanol (5000 ppm)
- *NDEA standard solution* in Methanol (100 ppm)

Internal Reference Standard Stock Solution (as purchased)

- *NDMA-d6 standard solution* in Methanol (1000 ppm)

Diluted standard solutions

***NDMA standard solution* (200 ppm):**

Transfer 800 µl of *NDMA reference solution* (5000 ppm) into a 20 mL volumetric flask, dilute to volume with methanol.

***Diluted standard solution* (NDMA: 40 ppm, NDEA: 20 ppm):**

Transfer 800 µl of *NDMA standard solution* (200 ppm) and 800 µl of *NDEA reference solution* (100 ppm) into a 4 mL volumetric flask, dilute to volume with methanol.

***Internal standard solution-1* (20 ppm):**

Transfer 500 µl of *NDMA-d6 standard solution* (1000 ppm) into a 25 mL volumetric flask, dilute to volume with methanol.

***Internal standard solution-2* (0.2 ppm):**

Transfer 5 ml of *NDMA-d6 standard solution* (20 ppm) into a 500 mL volumetric flask, dilute to volume with methanol.

Calibration solutions

STD-12:

Transfer 500 µl of *Diluted standard solution* (NDMA: 40 ppm, NDEA: 20 ppm) and 50 µl of *Internal standard solution-1 (20 ppm)* into a 5 mL volumetric flask, dilute to volume with methanol. Mix well.

STD-7:

Transfer 1000 µl of *STD-12* into a 20 mL volumetric flask, dilute to volume with *Internal standard solution-2* (0.2 ppm). Mix well. This solution will be used for the system suitability test and system drift check.

STD-11:
1:1 dilution of *STD-12* with *Internal standard solution-2*.

STD-10:
1:1 dilution of *STD-11* with *Internal standard solution-2*.

STD-9:
1:1 dilution of *STD-10* with *Internal standard solution-2*.

STD-8:
3:2 dilution of *STD-9* with *Internal standard solution-2*.

STD-6:
1:1 dilution of *STD-7* with *Internal standard solution-2*.

STD-5:
1:1 dilution of *STD-6* with *Internal standard solution-2*.

STD-4:
2:3 dilution of *STD-5* with *Internal standard solution-2*.

STD-3:
1:1 dilution of *STD-4* with *Internal standard solution-2*.

STD-2:
1:1 dilution of *STD-3* with *Internal standard solution-2*.

STD-1:
2:3 dilution of *STD-2* with *Internal standard solution-2*.

Concentration of calibration solutions:

Description	NDMA concentration (µg/mL)	NDEA concentration (µg/mL)	NDMA-d6 concentration (µg/mL)
STD-1	0.002	0.001	0.2
STD-2	0.005	0.0025	0.2
STD-3	0.01	0.005	0.2
STD-4	0.02	0.01	0.2
STD-5	0.05	0.025	0.2
STD-6	0.1	0.05	0.2
STD-7	0.2	0.1	0.2
STD-8	0.3	0.15	0.2
STD-9	0.5	0.25	0.2
STD-10	1	0.5	0.2
STD-11	2	1	0.2
STD-12	4	2	0.2

For NDMA, *STD-1* to *STD-6* are used as working range from 0.002 - 0.1 µg/mL, *STD-6* to *STD-12* are used as working range from 0.1 - 4.0 µg/mL.

For NDEA, *STD-1* to *STD-5* are used as working range from 0.001 - 0.025 µg/mL, *STD-5* to *STD-11* are used as working range from 0.025 - 1.0 µg/mL.

The working ranges of NDMA and NDEA can be adjusted as needed.

Sample Preparation

For finished product:

Weigh NLT 20 tablets and calculate average tablet weight. Carefully grind NLT 20 tablets into fine powder using a mortar and pestle.

Prepare triplicate samples for each product. Accurately weigh an amount equivalent to 250 mg of drug substance of the homogenized sample powder into a screw cap round bottom glass tube.

Using an automatic pipette, add 5 mL of *NDMA-d6 internal standard solution-2* to each sample tube. Tightly cap the tubes, sonicate for 5 min, and then vortex the rack of tubes on the multi-tube vortex mixer at 2000 rpm for five minutes. Centrifuge the tubes for at least five minutes at 1500 rpm. Carefully remove the tubes from the centrifuge. Use a Pasteur pipette to transfer an aliquot from each tube to a 2 mL GC vial and cap.

Note: Method accuracy was assessed by recovery studies. Valsartan, Irbesartan, and Losartan finished products were spiked with reference standard solution in the following way:

For samples with NDMA above 0.3 ppm and/or NDEA above 0.08 ppm:
Spike sample solution with the reference standard solution at concentration level close to sample concentration and calculate recovery.

For samples with NDMA below 0.3 ppm and/or NDEA below 0.08 ppm:
Spike sample solution with *STD-3* (1:1) to get solution containing 0.05 ppm of NDMA and 0.025 ppm of NDEA. Check S/N and calculate the LOD and LOQ.

For drug substance:

Prepare triplicate samples for each substance. Accurately weigh 250 mg of the homogenized sample powder into a screw cap round bottom glass tube.

Continue as per the instructions above for finished product. Spiking to determine method accuracy is recommended.

6. Instrument Operating Parameters:

Suggested GC parameters:

Injector Settings:

Injector Mode:
Pulsed Splitless

Injector temperature:
240 °C

Flow rate:
1.8 mL/min

Septum Purge Flow:
3 mL/min

Purge Flow:
50 mL/min after 0.75 minutes

Injection volume:
2.0 µL

Oven Program:

Initial Temp: 60°C

Hold: 2 min

Ramp #	Rate (°C /min)	Final Temp (°C)	Hold Time (min)
1	5	130	0
2	40	240	5
Total Run Time: 24 min			

Suggested MS settings

MS Transfer Line (Aux. Temp):
250 °C

Ion Source:
EI

Source Temperature:
250 °C

Solvent Delay:
6 min

Stop time:

15 min

Quench gas:
Helium at 2.25 mL/min

Collision gas:
Nitrogen at 1.5 mL/min

MS-MS parameters:

Analyte	Retention time (min)	Segment	Retention time window (min)	Precursor ion (*m/z*)	Product ion (*m/z*)	CE (V)	Resolution	Dwell (ms)
NDMA-d6 (ISTD)	7.8	1	7.5-8.1	80	50	5	wide/wide	100
NDMA	7.8	1	7.5-8.1	74	42	15	wide/wide	100
				74	44	4		100
NDEA	12.7	2	12.4-13.0	102	44	12	wide/wide	150
				102	85	2		150

7. System Suitability

The coefficient of determination (R^2) for each calibration curve is NLT 0.995.
The signal-to-noise of the *STD-1* (NDMA = 0.002 µg/mL; NDEA = 0.001 µg/mL) solution should be NLT 10.

8. Calculation

Construct calibration curves for NDMA and NDEA by plotting the ratio of response factor (NDMA or NDEA peak area divided by internal standard peak area) against standard concentration (µg/mL). Using the slopes and intercepts of the calibration curves, determine the content of NDMA and NDEA in each sample using the following equations.

For finished product:

The results, in ppm relative to the declared amount of sartan drug substance in the product, are given by:

Equation 1

$$(ppm) = [(y-b)/m] \times AVG_{wt} \times V \div Wt_{spl} \div LC$$

Where,

y =
Ratio of Peak Area of NDMA or NDEA to Peak Area of NDMA-d6

b =
intercept of the linear curve

m =
slope of the linear curve

Wt_{spl} =
sample weight (g)

AVG_{wt} =
average tablet weight (g)

LC =
label claim of sample (g)

V =
5 mL (volume)

▶ Equation 1 - Text Description

For drug substance:

The results, in ppm relative to the drug substance being tested, are given by:

Equation 2

$$(ppm) = \left[\frac{y-b}{m}\right] \times V \div Wt_{spl}$$

Where,

y =
Ratio of Peak Area of NDMA or NDEA to Peak Area of NDMA-d6

b =
intercept of the linear curve

m =
slope of the linear curve

Wt_{spl} =
sample weight (g)

V =
5 mL (volume)

▶ Equation 2 - Text Description

9. LOD and LOQ results

LOD/LOQ can be calculated using the S/N of the spiked sample solution (spiked with *STD-3* at 1:1).

Theoretical LOD/LOQ:

If no spiked results are available, the theoretical LODs and LOQs can be calculated by using the S/N of *STD-1* (NDMA: 0.002 µg/mL; NDEA 0.001 µg/mL).

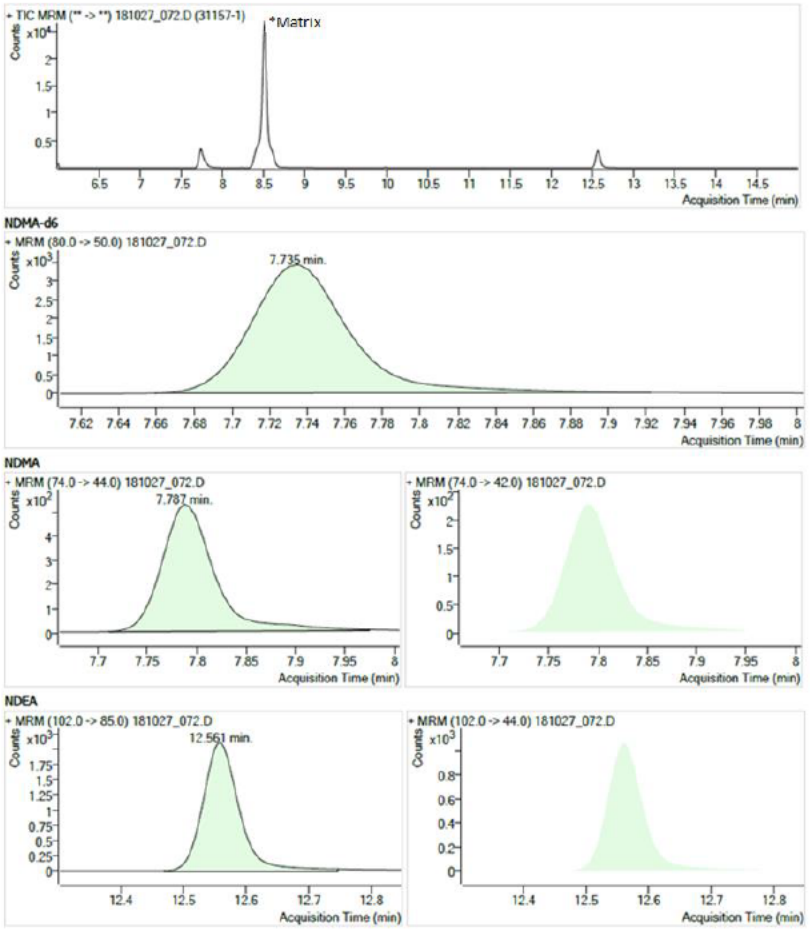
For reference, the theoretical LOD/LOQ results at Health Canada are as follows:

Table: S/N of NDMA and NDEA of *STD-1*.

	NDMA				NDEA			
Drug substance conc. µg/mL	**µg/mL**	**S/N**	**LOD (calc.) ppm**	**LOQ (calc.) ppm**	**µg/mL**	**S/N**	**LOD (calc.) ppm**	**LOQ (calc.) ppm**
50	0.002	74	0.002	0.0054	0.001	55	0.002	0.0073

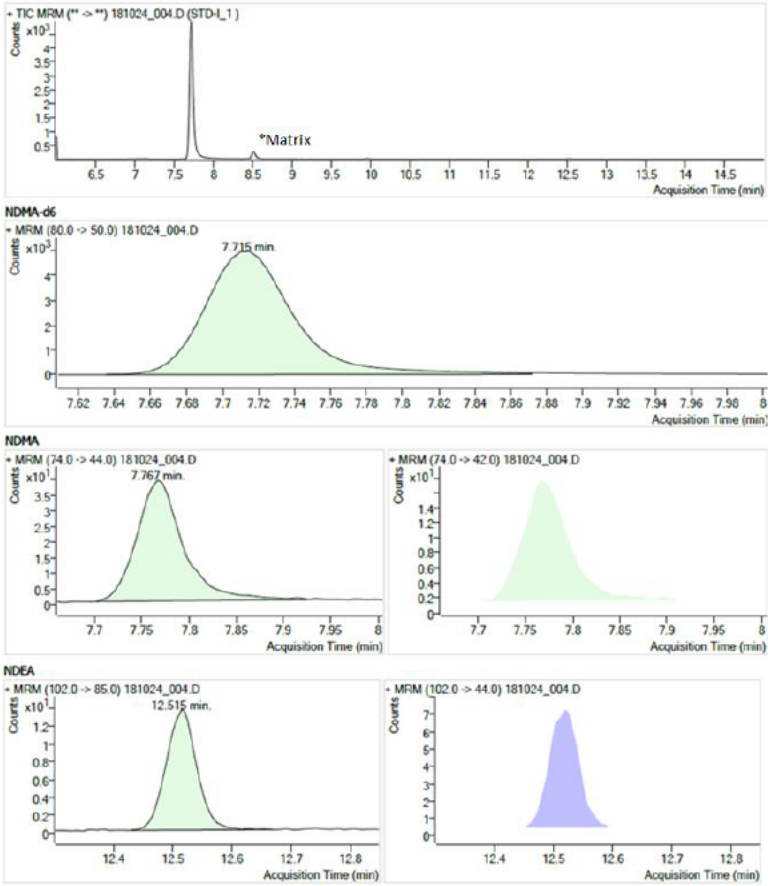
10. Sample Chromatograms

Figure 1: Chromatogram of sample with NDMA and NDEA detected.



▶ Figure 1 - Text Description

Figure 2: Chromatogram of *STD-1*.



▶ Figure 2 - Text Description

The United States Food and Drug Administration (FDA) and the European Directorate for the Quality of Medicines (EDQM) have also published methods to detect NDMA and NDEA:

- US FDA methods
- EDQM methods

Health Canada Communications

- Health Canada information update (2019-04-18): Auro Pharma Inc. voluntarily recalls one lot of Auro-Irbesartan HCT tablets because of nitrosamine impurity
- Health Canada information update (2019-03-14): Pro Doc Limitée voluntarily recalls two lots of irbesartan drugs because of nitrosamine impurity
- Health Canada information update (2019-03-09): Multiple Losartan-containing drugs voluntarily recalled because of potential for nitrosamine impurity
- Health Canada information update (2018-12-20): Health Canada releases test results of certain sartan drugs
- Health Canada information update (2018-11-28): Mylan-Valsartan medications voluntarily recalled as a precaution due to an impurity
- Health Canada information update (2018-10-02): Health Canada finds Zhejiang Huahai Pharmaceuticals site non-compliant with requirements for the manufacture of drug ingredients
- Health Canada information update (2018-09-13): Health Canada advises of a second impurity linked to recalled valsartan drugs
- Health Canada information update (2018-09-10): Health Canada updates Canadians on estimates of health risks for recalled valsartan drugs containing NDMA
- Health Canada information update (2018-08-18): Teva Canada expands recall of valsartan drugs to include additional lots, as a precaution
- Health Canada advisory (2018-07-09): Several drugs containing valsartan being recalled due to contamination with a potential carcinogen

Date modified:
2019-04-29